REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 1 has been amended to make an editorial change, i.e., to move the characterizing clause at the very end thereof into step (d). Applicants do not believe this change introduces any new matter. An early notice to that effect is earnestly solicited.

Also, claim 1 has been amended to specify that the incubation time of the suspension containing T cells with the protein fragment or fragments is sufficiently short so that selection and proliferation of stimulated T-cells do not occur. Applicants also do not believe this change introduces any new matter. An early notice to that effect is also earnestly solicited.

Further on this point, the present invention aims in one embodiment at providing a method allowing the determination which protein fragments of an antigen are capable of stimulating the highly variable T cell repertoire contained in freshly isolated blood of a patient (cf. page 4, last paragraph). The specification mentions that the inventive method is less susceptible to interference from culture conditions, selection due to culturing and the selecting of specific T cell clones than conventional methods. As a result, "a representative picture of T cells in general and T cells stimulated by protein fragments can be established by the method" (cf. page 8, 2nd paragraph, last sentence).

To allow for this representative picture, it is essential that the incubation time with the protein fragment is sufficiently short so that selection and proliferation accompanied by elimination of T cells is avoided (cf. page 5, 2nd paragraph). This is an important requirement, because any of these factors affects the T cell composition and, thus, the potential of the claimed method to indicate whether a given protein fragment is capable of stimulating a T cell in the patient's T cell population. For example, *proliferation* will add T cells which can be stimulated, while *elimination* will remove T cells. In this regard, it must be stressed that *elimination* of individual clones from the repertoire of T cells is generally observed as a consequence of stimulating a patient's T-cell population and can occur concomitant to or after T cell proliferation. Therefore, if incubation is sufficiently short so that selection and proliferation are avoided, as required by amended claim 14, elimination would necessarily also be avoided. Hence, deleting the reference to elimination of stimulated T cells does not add any new matter to the application as filed.

Finally, the dependency of claim 17 has been changed to "16" to provide antecedent basis for "class I" and "class II."

Turning to the substantive issues, claim 14 was objected to as being confusing. In response, Applicants have adopted the Examiner's helpful suggestion and incorporated the "characterizing" end portion of the claim into step (d).

Claims 14-21 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicants remind the Examiner that claims are not to be read in a vacuum, but in the light of the specification of which they are apart. Any person having ordinary skill in the art would understand that, in the context of the present invention, step

(b) does not refer to nor require a physical subdivision of the antigen into protein fragments, but, rather, to a mental or calculated subdivision of the antigen into such protein fragments. In other words, a person having ordinary skill in the art would understand that in step (a) the amino acid sequence of the antigen is established, then in step (b) a mental or calculated subdivision of the antigen into protein fragments is made and then in step (c) the protein fragments are physically made according to the mental or calculated subdivision by synthesizing the protein fragments or by cleaving the antigen into the protein fragments. Consequently, a person having ordinary skill in the art, reading the entire claim in the proper context and in the light of the accompanying specification, would correctly understand that step (b) is correctly positioned before step (c). Thus, Applicants respectfully submit there is no indefiniteness.

Claims 14 and 16-21 were rejected under 35 USC § 102(a) as being anticipated by Yanagisawa et al. ("Yanagisawa"), *International Immunology, 9(2):* 227-237 (1997). In response, Applicants would remind the Examiner that anticipation requires that each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference, and, further, the absence in the prior art reference of even a single one of the claim elements is sufficient to negate anticipation. *In re Robertson,* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). As amended, the claims require that the incubation time is so short that selection and proliferation of stimulated T-cells do not occur. Yanagisawa's method involves exposing primed T cells to protein fragments and measuring cytokines and cell proliferation ***after 72h,*** i.e. at a point in time when T cell proliferation ***has clearly occurred.*** Since the instant claims require selection and

proliferation of stimulated T cells do *not* occur, Yanagisawa's method cannot anticipate the instant claims.

Claims 14-21 were rejected under 35 USC § 103(a) as being obvious over Picker et al., *Blood, 86(4):* 1408-1419 (1995), and Yanagisawa. In response, Applicants point out that this rejection was dependent upon Yanagisawa anticipating the main claim 14, which, as noted above, is not, in fact, the case. Thus, the Examiner finds that a person having ordinary skill in the art would have found it obvious to use Picker's flow cytometry method in Yanagisawa's epitope mapping method. However, as noted above, Yanagisawa's method involves T cell proliferation, which is not permitted by the instant claims. Nothing in Pickering teaches or suggests modifying Yanagisawa's method to avoid T cell proliferation. Accordingly, the combined Pickering-Yanagisawa method would be characterized by T cell proliferation that is not permitted by the instant claims. Consequently, the combination of Pickering and Yanaigisawa does not make out a *prima facie* case of the obviousness of any of the current claims.

Further, the inventive method differs from Yanagisawa's method in two aspects, i.e. by measuring cytokines within or attached to the membrane of stimulated T cells and by measuring these cytokines at a point in time when elimination of stimulated T cells has not yet started. The technical effect of measuring cytokines prior to selection and proliferation of stimulated T cells must, in Applicants' view, be considered as preserving T cell clones, which would otherwise not be detectable in the patient's T cell population, either because they are underrepresented or physically lost from the T cell population. Hence, the inventive method has the potential of detecting additional T cell clones. Yanagisawa is silent on this issue, i.e. Yanagisawa does not mention the danger that T cell

clones may be eliminated if the primed T cells are analysed on day 3 or later after antigenic challenge. Therefore, the skilled person had no reason to modify Yanagisawa's method by measuring T cell activation earlier, i.e. at a point in time when selection and proliferation had not yet occurred. Moreover, even if the Examiner is right and the skilled person recognized the simplicity and overall availability of the detection technique of Picker, and, simply for this reason, would have modified the method of Yanagisawa, by replacing the ELISA-based cytokine detection method with the FACS-based detection method of Picker, this would still not result in the inventive method. In this regard, Applicants remind the Examiner that the present claims require that cytokine identification is performed at a point in time when selection and proliferation of stimulated T cells has ***not*** yet occurred. Again, the skilled person had no reason to modify Yanagisawa's method, i.e. to measure cytokines at an *earlier* point in time. The fact that Picker's method allows measuring cytokines at this early point in time after antigenic challenge does not provide this reason for modifying the method of Yanagisawa, since Picker's method is used for a completely different purpose, in particular ***not*** for mapping of T cell epitopes. Therefore, a combination of Yanagisawa and Picker would not render any of the present claims *prima facie* obvious to persons skilled in the art.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

NORRIS MCLAUGHLIN & MARCUS, P.A.

By /Kurt G. Briscoe/

Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue - 8th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844